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ORIGINAL ARTICLE

The effect of the antioxidant N-acetylcysteine on cholinesterase activity in the brain and blood during Pirimiphos methyl poisoning in the course of treatment with atropine alone, and with atropine and obidoxime

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Abstract

Introduction and Objective. The antioxidant N-acetylcysteine (NAC) may help in the treatment of organophosphates poisoning, including Pirymiphos methyl (PM). However, there is no information on the effect of NAC on target cholinesterases during the core treatment with atropine and obidoxime after acute and chronic exposure to PM. The impact was investigated of NAC on the functional status of target cholinesterases in the brain and blood during treatment with atropine (ATR) and/or obidoxime (OBID) in PM-induced toxicity.

Material sand Method. All experiments were performed on Male Swiss mice. The animals were intoxicated with PM and treated with OBID and/or ATR with or without and NAC, in various combinations (with 2–3 drugs) used simultaneously after intoxication. Total acetylcholinesterase activity (AChE) in brain and blood and plasma butyrylcholinesterase activity (BChE) were monitored at 2 and 72 h after intoxication. Enzyme activity was determined using Ellman's colorimetric method.

Results. The applied therapies with OBID, ATR and NAC in various configurations significantly reactivated PM-inhibited AChE in the brain and erythrocytes and the BChE in the plasma. The benefits of NAC administration in combination with ATR and/or OBID therapy have also been reported to restore AChE activity in the brain. NAC may reduce the dose of ATR in the treatment of PM poisoning.

Conclusions. Adjunctive treatment offered by NAC can reduce or prevent the deleterious effects against PM-induced toxicity. Therefore, NAC remains a strong candidate for adjunct treatment for OP-poisoning, including PM, although additional preclinical and clinical studies are needed.

Key words

pirimiphos-methyl poisoning, N-acetylcysteine, atropine, obidoxime, activities of AChE and BChE, mice

INTRODUCTION

Pirimiphos-methyl (PM) is an effective intragastric and contact insecticide against insect pests. It is a broad-spectrum, non-cumulative organophosphate compound (OP) widely used globally. The major PM use is the post-harvest control of insects by spraying wheat, barley and oat grains during storage, as well as in pre-harvest cleanup of fruits and vegetables, and for protecting the structural surfaces in empty grain storage facilities [1]. PM is also used for the control of mosquitoes and flies for public health purposes, e.g. for use as a mosquito parricide in drinking-water. The World Health Organization (WHO) recommends PM for use as Indoor Residual Spraying (IRS) and insecticidal-treated nets (ITNs) for mosquitoes control as the major important tools in malaria disease elimination in Africa [2].

The toxicity of PM is mainly due to the phosphorylation of the enzyme acetylcholinesterase (AChE) at cholinergic synapses, which is inhibited by the OP. As a result, acetylcholine (ACh) accumulates in the synaptic cleft of sympathetic and parasympathetic preganglionic synapses, central synapses and skeletal muscle afferent nerve endings, and stimulates cholinergic (muscarinic and nicotinic) receptors, which in turn causes enhancement and prolongation of cholinergic effects, depolarization blockade (acute cholinergic crisis), muscle weakness, seizures, coma, and respiratory failure [3]. PM (containing a P=S double bond) prior to phosphorylation is transformed into its oxon-variant via P450-mediated desulfurization, yielding pirimiphos-methyl-oxon. Similar to AChE in the nervous and neuromuscular systems, the circulating enzyme butyrylcholinesterase (BChE) is also a target of phosphorylation and inhibition by PM [4].

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Basic, traditional treatment for PM poisoning, as with other OPs, is based on the administration of the muscarinic receptor's antagonist (atropine), reactivators of inhibited cholinesterase (an oximes), and anticonvulsant benzodiazepines, such as diazepam [5]. Unfortunately, although the existing treatment regimen is useful, these antidotes have serious adverse effects and do not counteract all toxic effects [6]. Recently, oxidative stress has been proposed to play a direct or indirect toxic role in acute OP-s poisoning. Extensive studies have confirmed that exposure to a wide range of OPs increases the production of reactive oxygen species (ROS) and free radical-mediated changes in endogenous antioxidant enzymes, as well as lipid peroxidation [7]. Thus, the toxicity generated by OPs, including PM, can be counteracted by antioxidants such as N-acetylcysteine (NAC). In fact, numerous studies have confirmed that NAC treatment prevents and/or inhibits the oxidative processes as measured by various oxidative stress biomarkers [8].

NAC is the n-acetyl derivative of the natural amino acid L-cysteine. Previously, this compound was used as a mucolytic agent and as an antidote for acetaminophen (paracetamol; APAP) poisoning. Since the 1980s, NAC has been used in disease therapy where oxidative stress is involved in the pathogenesis and development of disease symptoms, such as mercury, arsenic and *Amanita phalloides* mushroom poisoning or carbon tetrachloride hepatotoxicity [9, 10]. Moreover, NAC is a precursor of L-cysteine, which affects the biosynthesis of the antioxidant glutathione, increasing its level in the body, supports detoxification and acting directly as a scavenger of free radicals [11]. NAC also has been proposed as an adjunct therapeutic agent for a safe and well-tolerated drug treatment for some disorders, such as liver cancer, haemodialysis, asthma, Alzheimer and Parkinson diseases [11]. These results confirm, that NAC may be used as an adjunct therapeutic agent for a range of xenobiotic-induced toxicities characterized by the generation of free oxygen radicals [12].

There is very little and unsatisfactory information on the effect of NAC on the functional status of both AChE and BChE during the treatment of OP-s poisoning. Therefore, the aim of this study is to investigate the impact of NAC on the functional status of both AChE in brain tissue and BChE in blood during treatment with atropine and obidoxime after acute and chronic exposure to PM. To the best of the authors' knowledge, this has not been previously examined.

MATERIALS AND METHODS

Animals. All experiments were performed on Male Swiss mice (n=144, weighing 22–26 g, 6–8 weeks old) supplied by a licensed dealer (T. Górzkowska, Warsaw, Poland). Animals were housed in colony cages (per 12 mice each) under controlled conditions (ambient temperature 21 °C ± 2 °C, humidity 50 ± 10%, with a 12-hour light-dark cycle with the light on at 06:00). The mice had access to food pellets and water *ad libitum*, throughout the whole study. After one week of acclimation, the mice were randomly divided into experimental groups consisting of 8 mice each, using a blind method. Each mouse was used only once.

The local Ethics Committee for Animal Experiments at the University of Life Sciences in Lublin approved all animal care and experimental procedures (License No. 55/2020).

Drugs and preparation of solution. Pirimiphos-methyl (PM; O,2-diethylamino-6-methylpirimidin-4-yl-O,O-dimethyl phosphor-thioate); N-acetylcysteine (NAC); obidoxime chloride (OBID; 1.1′-oxybis (methylene)-bis (4-hydroxyiminomethyl-pirydinum dichloride); atropine (ATR; atropine sulfate); propionyl thiocholine iodide; (2-mercaptoethyl) trimethylammonium iodide propionate]); eserine (physostigmine salicylate salt); 5.5-dithiobis-2-nitro-benzoic acid (DTNB) were purchased from Merck (Life Science, Germany).

The 'Mix for PM' mixture: DMSO (dimethyl sulfoxide) PEG-400 (polyethylene glycol 400) and Tween-80 were obtained from Sigma (St. Louis, MO, USA). All substances used were of the highest available chemical purity.

PM was dissolved in a 'Mix for PM' mixture consisting of DMSO, PEG-400 and distilled water with Tween-80 (2:3:5 v/v). N-acetylcysteine, obidoxime, atropine were dissolved in the saline.

Treatment procedure. All mice were randomly divided into two groups: an acute poisoning procedures group, (APG group, n=96 mice) and a subacute poisoning procedures group (SPG group, n=48 mice). Next, the mice in the APG group were randomly divided using a blind method into: control group, pirymiphos-methyl group (PM) and seven subgroups according to treatment: NAC (T1:PM+NAC), ATR (T2:PM+ATR); ATR+NAC (T3:PM+ATR+NAC); OBID (T4:PM+OBID); OBID+ATR (T5:PM+OBID+ATR); OBID+NAC (T6:PM+OBID+NAC); OBID+ATR+NAC (T7:PM+OBID+ATR+NAC). The SPG group was divided into control, PM and PM+NAC groups.

Mice from the APG group were given PM suspension (0,5 LD50−620 mg/kg body weight, b.w.) dissolved in mixture 'Mix for PM' by gavage and next, five minutes after PM were administered of NAC (150 mg/kg b.w.), ATR (10 mg/kg b.w.) and OBID (50 mg/kg b.w.), used intraperitoneally (i.p) dissolved in saline in the various combinations appropriate to the subgroup.

The SPG group was divided into control, PM and PM+NAC groups. These mice were treated with saline (control), or PM in dose of 0.1 LD50−140 mg/kg b.w. PM (PM group) or PM and NAC in a dose of 150 mg/kg b.w., daily for 14 days.

Mice from the control groups received the appropriate amount of the proper 'Mix for PM' solvent.

Tissue collection. Following cervical dislocation, the animals were decapitated at two, 72 h after PM poisoning (for the APG group) and two hours after the last PM injection (for the SPG group); samples of blood of approximately 0.5 mL were collected into heparinized Eppendorf tubes. At the same time, whole brain samples were rapidly removed from skulls, placed on ice-cold glass slides, weighed, and then stored in plastic tubes at -82 °C for assays.

Blood samples were analyzed immediately after collection. The brains were homogenized using Abbott buffer (2:1, v/w; Abbott Laboratories, North Chicago, IL, USA) in an Ultra-Turrax T8 homogenizer (IKA Werke, Staufen, Germany) the next day. The homogenates were centrifuged at 10,000g for 10 min., and the supernatant samples used for analysis.

Determination activity of BChE (EC 3.1.1.8) and AChE (EC 3.1.1.7). Plasma BChE activity and both erythrocyte and brain AChE activity were determined by the modified Ellman spectrophotometric method (Ellman et al., 1961),

using acetylthiocholine iodide as the substrate and eserine as the inhibitor, and a buffered DTNB solution. Erythrocyte AChE activity was determined from the difference in whole blood and plasma choliesterase activity. The absorbance of the reaction mixture was determined using the BioTec ELX800 Absorbance Microplate Reader (BioTek Instruments, USA). This method and procedure have been described in detail in an earlier study by the authors [13].

Statistical analysis. The results are presented as the mean value ± standard deviation (SD). The significance of differences was assessed using either a two-tailed, unpaired Student's t-test or a two-way analysis of variance (ANOVA) followed by the *post-hoc* Tukey test. Differences were considered statistically significant at $p < 0.05$. All data analysis was performed using GraphPad Prism 9.0 software.

RESULTS

As shown in Figure 1, the control activities of AChE in mouse brain and erythrocyte were (mean ± S.E.M.; n=16) 8.099 ± 1.127 and 0.494 ± 0.082 IU/g, respectively. Plasma activity of BChE in control mice was 1.21± 0.098 IU/g.

At 2h after PM exposure, there was a significant ($p<0.001$) decrease in the mean values of brain and erythrocyte levels of AChE and the BChE activity in plasma in treatment groups, compared to controls.

After the next 72 h after PM, the values of both enzymes increased significantly ($p<0.001$), but did not reach the control activities prior to the poisoning.

Effect of N-acetylcysteine on cholinesterases status in both blood and brain of mice during acute PM exposure and atropine treatment

There was no effect of NAC and NAC+ATR on PM toxicity or both AChE and BChE activity in the brain and blood of mice when using this therapy. This effect was also maintained 72 hours after PM administration (Fig. 2A-C).

Effect of N-acetylcysteine on cholinesterases status in both the blood and brain of mice during acute PM exposure and obidoxime and/or atropine treatment

As shown in Figures 3A-C, one-way ANOVA analysis was performed, showing significant differences among the experimental groups. Multiple comparison analysis by Tukey test (*post-hoc*) showed statistical significance among the experimental groups (Control vs. PM, PM vs. PM+T4-T7) at 2 and 72 hours during acute PM exposure.

The treatment with OBID and OBID+ATR caused a strong increase in BChE and AChE levels, at 2 hours during acute PM exposure.

Next, co-administration of NAC with OBID and OBID+ATR, immediately after PM poisoning, at 2 hours of poisoning, had no effect on the studied enzymes (PM+OBID vs. PM+OBID+NAC and PM+OBID+ATR vs. PM+OBID+ATR+NAC).

However, at 72 hours, NAC administered with OBID significantly increased the levels of AChE in mice brain tissue (Fig. 3C) in comparison to OBID alone.

Effect of N-acetylcysteine on cholinesterases status in both the blood and brain of mice during subacute PM exposure and NAC treatment. As shown (Fig. 4C), the treatment with NAC applied daily immediately after subacute poisoning with PM resulted in an increase in the level of brain AChE activity ($p=0.032$) in comparison to intoxicated and no treatment animals. It was also observed that daily NAC administration with PM in subacute poisoning did not restore plasma BChE activity, nor in both brain and erythrocyte AChE activity.

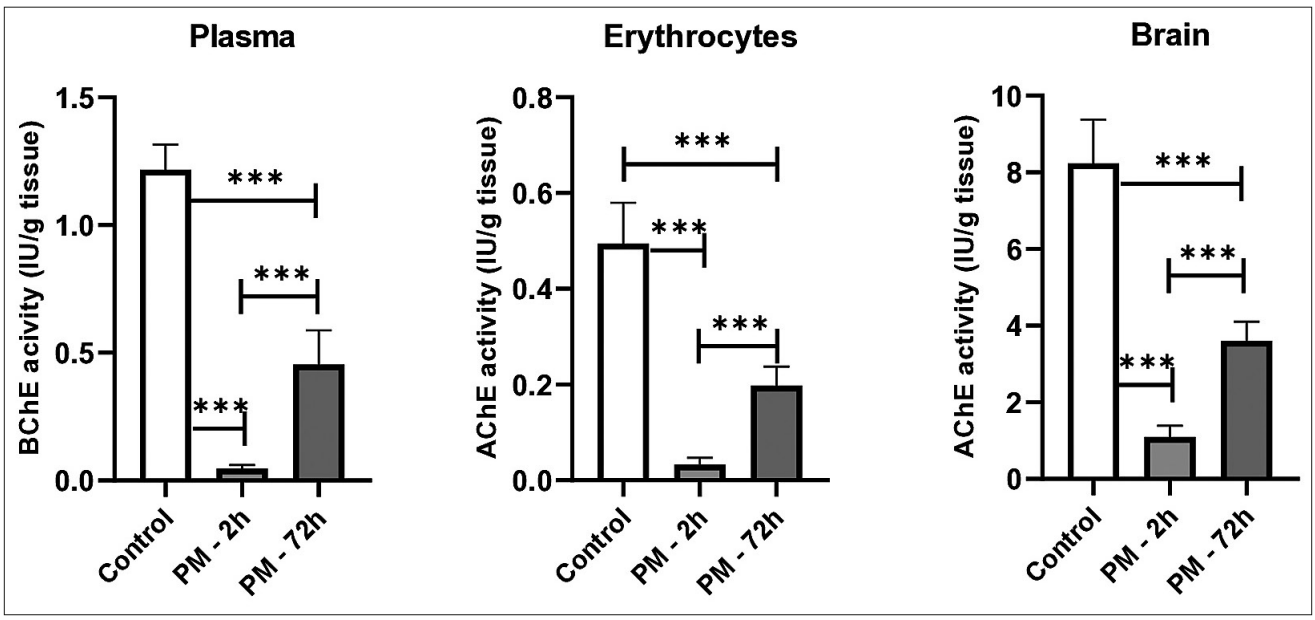

Figure 1. Effect of pirymiphos methyl on butyrylcholinesterase activity in plasma and acetylcholinesterase activity in erythrocytes and brain, 2 and 72 hours after administration.
The activity of butyrylcholinesterase (BChE) in plasma and acetylcholinesterase (AChE) in both erythrocytes and brain in mice treated with solvent (Mix for PM – control) or pPirymiphos methyl (PM, 620 mg/kg b.w., acute poisoning). Tissues were obtained 2 and 72 hours after solvent or PM injection. Data are expressed as the mean ± SEM of 8 or 16 (control) determinations. *** $p<0.0001$

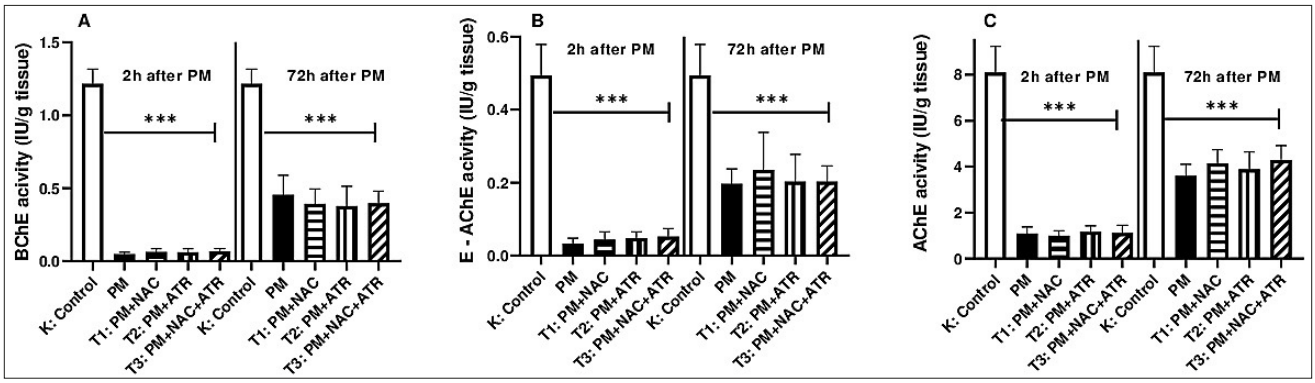

Figure 2. Effect of N-acetylcysteine on cholinesterases status during acute PM exposure and atropine treatment.
Activity of plasma butyrylcholinesterase (BChE) (A) erythrocyte acetylcholinesterase (E-AChE) (B) and brain acetylcholinesterase (AChE) (C) during treatment with N-acetylcysteine (NAC, 150 mg/kg, b.w) and atropine (ATR, 10 mg/kg, b.w.) in mice treated with solvent (Mix for PM – K-control) or pirymiphos methyl (PM, 620 mg/kg b.w). ATR and NAC were injected immediately after PM. Tissues were obtained 2 and 72 hrs after solvent or treatment injection. Data are expressed as mean ± SEM of 8 or 16 (control) determinations.
*** p<0.0001

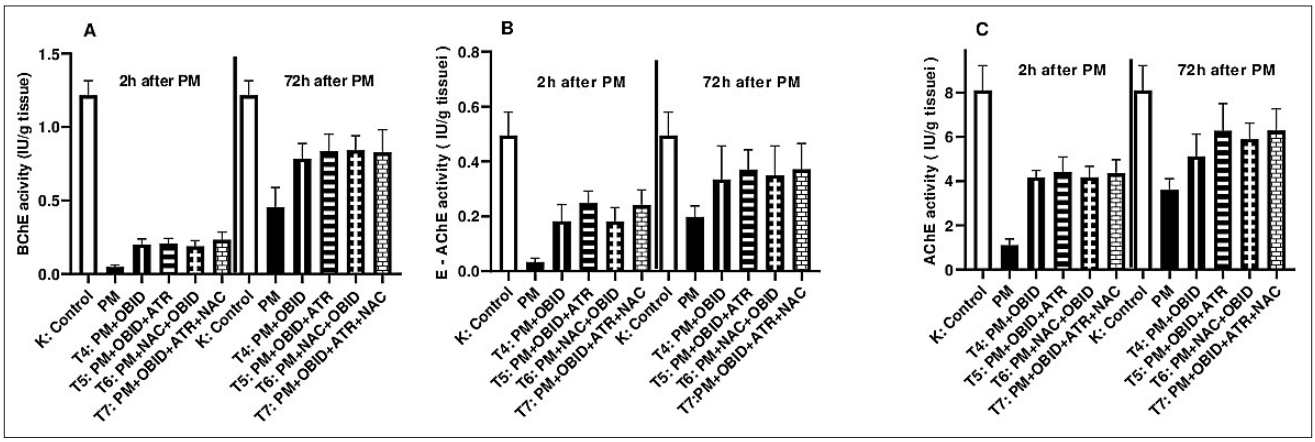

Figure 3. Effect of N-acetylcysteine on cholinesterases status during acute PM exposure and atropine or atropine and obidoxime treatment
Fig. A: p<0.001 for K/PM; K/T4-T7; PM/T4-T7 – 2h and 72h after PM;
Fig. B: p<0.001 for K/PM; K/T4-T7; PM/T4-T7; p=0,030 for T4/T5; p=0,041 for T5/T6 – 2h after PM and p=0.003 for K/T4-T5; p=0.013 for K/T7; p=0.047 for PM/T4; p=0.045 for PM/T5; p=0.001 for PM/T6; p=0.016 for PM/T7 – 72h after PM;
Fig. C: p<0.001 for K/PM; K/T4-T7; PM/T4-T7; p=0,043 for T4/T5; p=0,028 for T4/T7; p=0,033 for T5/T6; p=0.021 for T6/T7 – 2h after PM and p<0.001 for K/PM; K/T4-T7; PM/T5-T7; p=0.012 for T4/T6; p=0,028 for T4/T7 – 72h after PM;
Activity of plasma butyrylcholinesterase (BChE) (A) erythrocyte acetylcholinesterase (E-AChE) (B) and brain acetylcholinesterase (AChE) (C) during treatment with N-acetylcysteine (NAC, 150 mg/kg, b.w); atropine (ATR, 10 mg/kg, b.w.) and obidoxime (OBID, 50 mg/kg b.w.) in mice treated with solvent (Mix for PM – K-control) or pirymiphos methyl (PM, 620 mg/kg b.w). ATR, OBID and NAC were injected immediately after PM. Tissues were obtained 2 and 72 hrs after solvent or treatment injection. Data are expressed as mean ± SEM of 8 or 16 (control) determinations

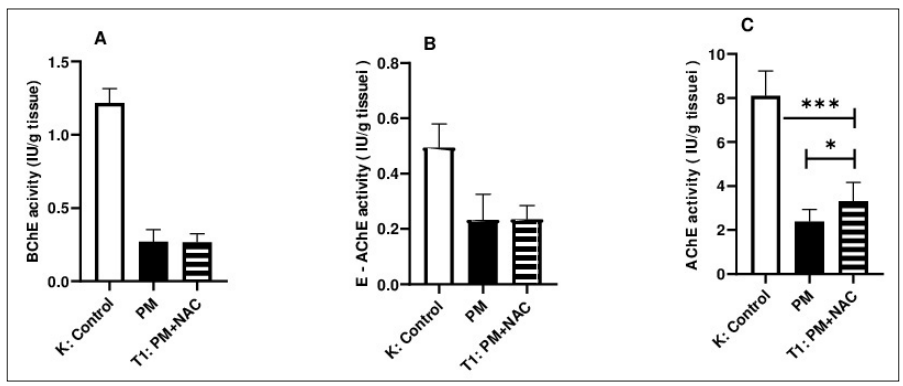

Figure 4. Effect of N-acetylcysteine on cholinesterase statusy during subacute PM poisoning.
Activity of plasma butyrylcholinesterase (BChE) (A) erythrocyte acetylcholinesterase (E-AChE) (B) and brain acetylcholinesterase (AChE) (C) during treatment with N-acetylcysteine (NAC, 150 mg/kg, b.w) in mice treated with solvent (Mix for PM – K-control) or pirymiphos methyl (PM, 140 mg/kg b.w). NAC were injected immediately after PM. Tissues were obtained 2 hours after the solvent or final treatment injection. Data are expressed as mean ± SEM of 8 or 16 (control) determinations.
* p = 0.032; *** p<0.001

DISCUSSION

The current study investigated the effects of NAC on the PM-induced both BChE and AChE activity inhibition in mouse blood and brain tissue during both intoxication, and intoxication and treatment with atropine and/or atropine together with obidoxime. The treatment guidelines for organophosphate poisoning, including PM, recommend prompt administration of atropine as the first-line antidote, oximes as a follow-up, and benzodiazepines for seizure control [5]. In recent years, NAC has gained increasing promise as an adjunctive therapeutic agent in these poisonings due to its ability to counteract oxidative stress generated by organophosphate compounds [12]. In fact, the results of previous work by the authors of the current study suggest that NAC significantly reduces the oxidative stress generated by PM, and may be a potentially effective therapeutic adjunct to treatment with both atropine and/or atropine in combination with obidoxime. It was also found that this treatment had no effect on the antioxidant properties of NAC [14].

However, a particular problem in interpreting the beneficial role of NAC as an adjunct to the treatment of PM-s poisonings is that there is no data about the effect of NAC on target cholinesterases during treatment. It is not known whether and what the effect of NAC is on both the toxicity of PM and the therapeutic effectiveness of routinely used treatment using ATR alone and ATR in combination with OBID, in the course of acute and subacute PM poisoning.

AChE is the major form of cholinesterases, found mainly in neurons and neuromuscular junctions, as well as in erythrocyte membranes [15]. The second form of cholinesterase – BChE, is an enzyme present in plasma, liver, cerebrospinal fluid and glial cells. It is assumed that BChE acts as a stoichiometric OP-s scavenger, and its inhibition does not appear to have significant physiological effects [16]. However, there are studies indicating that BChE may also play a role in the cholinergic neurotransmission and is involved in the functioning of the nervous system [17]. It is generally accepted that BChE is a reliable indicator of OPs exposure but not of the effects of poisoning [16]. However, measuring the degree of AChE inhibition is still a commonly used method to assess the effects of OPs exposure and the effectiveness of the therapy [18].

In the presented work, acute PM poisoning of mice resulted in the strong blocking of AChE and BChE activity in the blood and in the brain of animals with varying intensity. However, the results obtained for PM confirm the general view for OPs that individual compounds have a greater affinity for BChE, which is related to its greater inactivation than in the case of AChE in erythrocytes and the brain [19]. This indicates difficulties in crossing the physiological blood-brain barrier by PM, its different affinity for brain and erythrocyte AChE (e.g. by different molecular forms of AChE), and the effective neutralization of PM by BChE in plasma [19].

The dynamics of spontaneous reactivation and recovery of the active forms of enzymes after acute PM poisoning in the examined tissues were relatively slow. The recovery of total cholinesterase activity in the nervous system and blood depends mainly on the synthesis of new, active enzyme molecules. This process is long-term, and the results obtained confirm the data from other studies analyzing the reactivation of AChE in erythrocytes and the brain after poisoning with various OP-s [20]. It was found that NAC had no effect on the activity of AChE in the brain and erythrocytes or on the level of BChE in the plasma, compared to the activity of esterases in the acutely poisoned animals. However, in the case of subacute poisoning, 14 days administration of PM simultaneously with NAC already caused an effect on AChE in the mouse brain ($p=0.0325$), increasing its activity. The use of NAC may be useful in chronic exposure to OP-s, which causes various pathophysiological states due to long-term oxidative stress, including PM poisoning [21]. It can also be concluded that NAC showed a clear beneficial effect on AChE in terms of the toxicity of chlorpyrifos-ethyl and chlorpyrifos-methyl. However, NAC administration was not associated with a significant effect on BChE activity [22]. Additionally, Yurumez et al. demonstrated a beneficial effect of NAC against fenthion toxicity in mice and indicated that NAC may have prophylactic and therapeutic effects in OPs poisoning, significantly improving the survival of mice at higher NAC doses. However, they did not determine whether the improved survival was due to the antioxidant properties of NAC or another mechanism [23].

Next, the effect of NAC administration with and without ATR on blood and brain cholinesterases after acute PM poisoning was examined and compared. Analysis with the one-way ANOVA test of variance did not show significant differences in the distribution of AChE activity levels in the brain and erythrocytes and the level of BChE between the experimental groups of animals treated with NAC and ATR in different combinations at 2 and 72 h after PM administration. This fact indicates that replacing ATR with NAC, as well as administering NAC together with ATR at both monitored times, had a similar effect on PM toxicity and the effectiveness of this therapy, i.e. it did not affect the activity of the analyzed enzymes.

Recommendations regarding effective dosing leading to lung clearance and improvement of circulatory system function in the course of OPs poisoning differ significantly [24]. It is worth noting that when the dose of ATR is exceeded, serious adverse effects may occur [25]. Therefore, actions aimed at limiting the use of ATR are beneficial to health, especially in cases of poisoning treatment, where the administration of ATR alone is sufficient.

The obtained results indicate that the use of NAC in acute PM poisoning may be beneficial by limiting the dose of ATR, especially since NAC has a mucolytic effect and can reduce its secretion [26], which is very important in ZFO poisoning. Clinical data also indicate that the use of NAC may be responsible for reducing the need for ATR in OPs poisoning [12].

The administration of ATR alone to counteract the effects of OPs poisoning with a mild course is sufficient therapy. However, an integral part of the treatment of acute intoxications with OP-s the use of atropine in combination with oxime compounds, reactivators of inhibited AChE (e.g., OBID) [27]. Therefore, the effectiveness of the adjunctive treatment with NAC in acute PM poisoning was analyzed using OBID alone and OBID together with ATR. We found significantly higher activity of both BChE and AChE when using therapy with OBID, compared to treatment without the use of oxime in PM poisoning. This confirms the known reactivating properties of OBID in restoring the activity of cholinesterases inhibited by various OPs [27, 13]. NAC as an adjunct to the treatment with OBID and OBID+ATR caused no changes in BChE activity. Similarly, the administration of

NAC with OBID, in the initial period of intoxication, had no effect on increasing OBID activity or restoring AChE activity in the brain and erythrocytes.

However, the analysis for comparisons of selected therapeutic groups with OBID showed that 72 h after PM poisoning, NAC administered alone (or together with ATR) had a beneficial effect on OBID in the restoration of inhibited AChE activity in the brain in treated animals. This fact speaks in favour of the benefits that may result from the use of NAC in PM poisoning. The mechanism of the enhanced ability of OBID to restore AChE activity in the brain during PM poisoning by NAC is unknown, but it may result from the facilitation of OBID penetration into brain structures by NAC or from the properties of NAC associated with cholinergic receptors [12].

No comparative studies of the effect of NAC on the reactivation activity of oxime in OPs poisoning have been found. In a clinical study on 2 groups of patients poisoned with different OPs and treated conventionally with ATR, oxime and NAC or ATR and oxime, no differences in BChE activity were found. Similarly, the effect was also demonstrated in mice [12]. In another study, in acute paraoxon poisoning, the simultaneous use of pralidoxime (another oxime compound) and antioxidants (NAC, glutathione, ascorbic acid) provided better protection than pralidoxime alone, which, as the authors indicate, may result from the interference of antioxidants with the action of oxime. However, it is not known whether this protection was due to increased AChE activity or other mechanisms [21].

CONCLUSIONS

In this study, NAC was found to enhance the potential of OBID to reactivate PM-inhibited brain AChE. Therefore, this positive impact of NAC may prompts consideration for its inclusion into treatment protocols in cases of PM poisoning, but additional preclinical and clinical studies are needed.

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